

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 June 2003 (19.06.2003)

PCT

(10) International Publication Number
WO 03/049774 A1

(51) International Patent Classification⁷: A61K 031/045,
031/66, 047/42, A61P 25/04

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(21) International Application Number: PCT/AU02/01686

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:

13 December 2002 (13.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

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Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/049774 A1

(54) Title: TRANSDERMAL TRANSPORT OF COMPOUNDS

WO (57) Abstract: There is provided a topical formulation comprising an effective skin-penetrating amount of one or more phosphate derivatives of one or more pharmaceutical hydroxy compounds and an acceptable carrier.

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Transdermal Transport of Compounds

Field of the Invention

This invention relates to transdermal drug transport for the application of drug compounds and methods for improving dermal penetration of compounds.

5 Background of the Invention

In this specification, where a document, act or item of knowledge is referred to or discussed, this reference or discussion is not to be taken as an admission that the document, act or item of knowledge was at the priority date:

- (a) part of common general knowledge; or
- 10 (b) known to be relevant to an attempt to solve any problem with which this specification is concerned.

Therapeutic substances have been applied topically to the skin for many years. First reports date back to the Egyptians who applied ointments to the skin for healing. However, it was only in the late nineteenth century that some compounds 15 were discovered to be better absorbed through the skin than others. Since then, scientists have worked to determine the mechanisms controlling percutaneous absorption and how to manipulate these routes.

The skin is the largest organ of the body, which functions to protect the internal organs from external chemical, physical and pathological hazards. Normal skin is 20 divided into three layers: the epidermis, the dermis, and subcutaneous tissue. The outer cornified layer of the epidermis, the stratum corneum, possesses properties of strength, flexibility, high electrical impedance and dryness that retards penetration and proliferation of microorganisms. The stratum corneum is also the principle barrier to transdermal drug absorption. There is a layer of sebum 25 protecting the skin which has not commonly been considered to be a barrier to drug transport.

When travelling through the skin, a diffusing drug molecule has a number of potential transport routes available. These include appendageal such as eccrine, follicular or epidermal such as inter or intra cellular. Current theories regarding the 30 transport route point to two possible mechanisms: (i) passive transcellular and (ii) intracellular epidermal transport. Evidence also exists that active transport systems in the skin are important to regulate homeostasis and that this process operates to move compounds across membranes and throughout the dermis. Active transport mechanisms have not been considered or exploited as a drug 35 delivery pathway, as the absorption process is believed to be largely a permeation process.

Drugs are topically applied in a number of ways including ointments, patches, solutions, subcutaneous depots, poultices, plasters and transdermal delivery devices. Transdermal delivery devices are a subset of topical application which involves the drug penetrating the dermis in contrast to a mere topical application in which a drug acts on the surface of the dermis.

Transdermal delivery devices include diffusion controlled polymeric membrane reservoir delivery systems. Such devices, often in the form of patches, aim to maintain a constant rate of drug release over an extended period of time under steady state conditions, which is sometimes referred to as "zero-order release" or "zero-order kinetics". Such patches usually consist of one or more rate controlling membranes surrounding a drug solution operating to maintain a constant rate of drug release. This is generally achieved by using membrane devices, microcapsules, liposomes and hollow fibres in various polymeric materials including silicone rubber, ethylene vinylacetate, cellulose acetate, copolymers, polyurethanes and hydrogels.

Transdermal delivery has been recognized to offer several potential benefits including achieving similar blood levels as slow intravenous infusion without the inconvenience, better control of absorption and metabolism compared to oral administration, continuity of drug effect especially of drugs with short half lives, equivalent efficacy with reduced drug dosage by by-passing hepatic first pass elimination, lower risk of under or overdosing and better patient compliance through simplified dosage regime.

Transdermal delivery devices are useful for drugs that are difficult to deliver orally, have short half lives or need zero order. They are currently utilized to deliver drugs in a number of therapeutic areas ranging from but not limited to sex hormones in birth control and management of the menopause (Estraderm® by Ciba-Geigy, Oestradiol implants by Organon), gonadal hormones in anticancer therapy (Depo-Provera® by Pharmacia-Upjohn) analgesic subcutaneous depots in chronic pain control, nitrates in angina therapy (Deponit® by Pharma-Schwarz/Lohmann, Nitrodisc® by Searle, Nitro-Dur® by Key, and Transiderm-Nitro® by Ciba-Geigy, Frandol® by Yamanouchi), antiemetics in motion sickness and nausea (Scop® by Ciba-Geigy), and nicotine in smoking cessation therapy (Nicabate® by Marion Merrell Dow, Nicotinell® by Ciba-Geigy)

Transdermal estradiol administration, is a well established method for treating menopausal symptoms and hypogonadal conditions in adolescent females, but skin irritation has been reported in up to 17% of females using the patches.

Transdermal administration is preferred to oral administration because it avoids

hepatic first-pass metabolism as well as issues of metabolism and absorbance through intestinal walls. In addition, lower dosages can be administered compared to those used in oral therapy. Ideally, a physiologically active metabolite of estrogen would improve bioactivity, however, their highly lipidic nature makes

5 delivery extremely difficult to deliver.

A study by Morgan, TM., Parr, RA., Reed, BL. and Finnin, BC (1998). Enhanced transdermal delivery of sex hormones in swine with a novel topical aerosol. *J. Pharm. Sci.* 87(10): 1219-1225 investigated the transdermal delivery of testosterone and estradiol in pigs using a novel metered dose topical aerosol

10 containing a penetration enhancer padimate O. The volatile compounds in a drug solvent system containing a mixture of volatile and non-volatile solvents as a vehicle can evaporate from the skin creating a supersaturated solution on the skin surface in an attempt to stimulate drug absorption by creating a concentration gradient. One of the major problems of these systems is the difficulty in creating

15 systems that are reproducible since the rate and degree of volatile solvent evaporation will depend upon ambient conditions during application. Variability in absorption kinetics causes fluctuations in drug delivery and unreliable clinical efficacy.

Metered dose devices also require co-ordination and manual dexterity for efficient

20 use. The authors also claim that the dose system provides flexibility and can be moved around to provide a greater surface area of application. Further, it would still be necessary to move the dose around because the enhancer is an hydroxy cinnamate that damages the skin and causes irritation and erythema. Therefore,

25 this aerosol dosing system would offer no more clinical advantage than a patch containing enhancers.

Interest in transdermal drug delivery may be increasing but some fundamental limitations restrict broader application of the technology. The main limitations to use of transdermal deliverys is the rate of transport of the drug through the skin and patient compliance.

30 Not every drug can be administered transdermally at a rate sufficiently high enough to achieve blood levels that are therapeutically beneficial for systemic medication. Drugs with similar molecular weights and sizes for example may absorb across the skin at different rates. Fentanyl for example permeates the skin at 2 $\mu\text{g}/\text{cm}^2/\text{hr}$ compared to ephedrine at 200 $\mu\text{g}/\text{cm}^2/\text{hr}$. The large size of a

35 transdermal delivery system required for fentanyl would therefore be neither practical or economical despite the advantages of the administration route.

Skin enhancers and various formulation techniques have been developed to improve drug absorption through the skin. Skin enhancers can include compounds like capric acid, oleic acid, azone, decylmethyl sulfoxide and hydroxy cinnamates, that typically function to modify structure especially of the stratum corneum by dissolving the lipid matrix to improve permeability of drug compounds. Dermal absorption of progesterone for example increases by 143% when the stratum corneum is delipidized. The enhancement increases to 843% when the stratum corneum is totally eliminated. With such aggressive modification, commonly reported problems with repeated use of such systems are therefore evident, including contact dermatitis, reddening of the skin, itching and burning that requires movement of the patch, or application of the drug, around the body to prevent local irritation. The reddening is said to disappear within hours of removing the patch. But concern has been raised with respect to long term risk and safety with use of this type of transdermal delivery systems, mainly because increased drug permeability is achieved at the cost of damaging a fundamentally important protective layer of the skin.

Another limitation to transdermal delivery systems is the difficulty in formulating a drug compound that is both sufficiently lipid soluble to absorb through phospholipid membranes yet water soluble to move in the aqueous cytosol and usually hydrophilic suspension media. Drug molecules need to pass both lipophilic and hydrophilic barriers in traversing the skin. This is difficult to achieve and can slow dermal transport.

While improvements in formulation should therefore be considered it is also important to understand that rate of release and bioavailability of drug compounds from transdermal delivery systems can also be dependant upon the device geometry and the nature, thickness and area of the membrane used. Duration of release is believed to be governed by size of the drug reservoir and bioavailability of the drug compound. Mathematical models have been proposed to estimate the kinetics of drug release. Like all physiochemical mathematical approaches, biological factors are not always well described.

Subsequent strategies arising from such models aim to increase solubility and dissolution rate of drugs from dosage forms. Theoretically, these strategies make the drug more available for absorption through membranes, and involve techniques such as co-solvent addition, complexation, solid state manipulation of the membrane by skin enhancers and pro-drug modification. However, these mathematical approaches have been criticized for not being able to effectively generate descriptors for three dimensional features, such as hydrophobicity and

some electronic effects of drug interaction including hydrogen bonding.

Mathematical descriptors are also inadequate in describing various biological processes including dermal absorption, gastrointestinal absorption, distribution, metabolism and excretion. Current solutions arising from the mathematical model 5 are best described as two dimensional approaches to a three dimensional puzzle.

On this basis, design of current transdermal delivery systems is flawed and cannot account for all important dimensions of passive and active biological transport processes. Current strategies to improve transdermal therapy have not been 10 universally successful and there is scope for further improvement. In particular, there is a need for use of transdermal delivery systems capable of delivering a wider range of drugs.

Summary of the Invention

It has been found that phosphate derivatives of pharmaceuticals with hydroxyl groups surprisingly show faster transport through the skin when compared with the 15 transport of the parent pharmaceutical compound. This leads to useful topical formulations of pharmaceuticals such as creams, patches and spray on forms, that are therapeutically effective and do not risk the integrity of, or damage to, the skin.

According to the first aspect of the invention, there is provided a topical formulation comprising an effective skin-penetrating amount of one or more phosphate 20 derivatives of one or more pharmaceutical hydroxy compounds and an acceptable carrier.

This aspect of the invention also provides a transdermal delivery system comprising one or more phosphate derivatives of one or more pharmaceutical hydroxy compounds and one or more sustained release systems designed to alter 25 absorption kinetics in favor of zero order release.

The term "pharmaceutical hydroxy compounds" is used herein to refer to pharmaceutically active compounds selected from the group consisting of hydroxy compounds where the hydroxy group is not likely to be sterically hindered.

Examples of pharmaceutical hydroxy compounds include but are not limited to 30 narcotic analgesics such as morphine and levorphanol, non narcotic analgesics such as codeine and acetaminophen, corticosteroids such as cortisone, anaesthetics such as propofol, antiemetics such scopolamine, sympathomimetic drugs such as adrenaline and dopamine, antiepileptic drugs such as fosphenytoin, anti-inflammatory drugs such as ibuprofen, thyroid hormones and antithyroid drugs 35 including thyroxine, phytochemicals including α -bisabolol, eugenol, silybin, soy isoflavones, iridoid glycosides including aucubin and catalpol, sesquiterpene

lactones including pseudoguaianolide from *Arnica chamissonis*, terpenes including rosmarinic acid and rosmanol, phenolic glycosides including the salicylates salicin, saligenin and salicyclic acid, triterpenes taxasterol or α -lactucerol, and isolactucerol, *p*-hydroxyphenylacetic acid derivative taraxacoside, hydroquinone

5 derivatives including arbutin, phenylalkanones including gingerols and shagaols, hypercin, and acylphloroglucides including xanthohumol, lupulone, humulone and 2-methylbut-3-en-2-ol.

Specific examples of pharmaceutical hydroxy compounds are as follows:

Warfarin and coumarin derivatives	Dienestrol
	Epanolol
Acetophenazine	Esmolol
	Estradiol
Acyclovir	Estrone
Ganciclovir	Ethynylestradiol
Indinovir	Ethisterone
Lamivudine	Hexestrol
Penciclovir	Hydrocortisone
Ritinavir	Methylprednisolone
saquinavir	methyltestosterone
zalsitabine	
zidovudine	fluconazole
	dronabinol
Isosorbide mononitrate	Carbidopa
tacrolimus	
Adrenaline	Morphine
Chlorprenaline	Apomorphine and other narcotics
Atropine	Codeine
Denopamine	Naltrexone
Dobutamine	Pentazocine
Dopamine	phenazocine

Epinephrine	tramadol
Fenoterol	
Formoterol	Atenolol
scopolamine	Labetolol
	sotolol
	timolol
Doxefazepam	
Lorazepam	Dinoprost
temazepam	Epoprostenol
	Latanoprost
terfenadine	misoprostol
Iosartan	doxorubicin
	Daunorubicin
Desmopressin	Paclitaxel
Dextrothyroxin	Teniposide
Levothyroxine	Topotecan
	zorubicin
troglitazone	
	venlafaxine
Androstanolone	
clocortilone	Atorvastatin
Betamethasone	Fluvastatin
Cortisone	Lovastatin
Danazol	Pravastatin
simvastatin	Carbazochrome
	Carbuterol
	Carfenazine
Dipyridamole	Chenodeoxycholic acid

Dithranol	Chloral hydrate
Calipotriol	Chlorobutanol
	Chlorophenesin
	Cianidanol
	Cimetropium bromide
Ambroxol	Clidinium
Cefadroxil	Clofoctol
Cefamandole	Clopenthixol
Cefatrizine	Cyclobutyrol
Cefoperazone	Cyclamine
Cefpiramide	Cynarine
Clavulinic acid	Dezocine
Doxycycline	Dichlorophen
Latamoxef	Diflunisal
Meropenem	Dimercaprol
Metacycline	Diprophylline
Metronidazole	Dropazine
Minocycline	Edrophonium
Novoniocin	Elliptinium
Rolitetracycline	Eprozinol
Spectinomycin	ergometrine
tetracycline	etamivan
	etamsylate
	ethambutol
Ioperamide	etilifrine
	etofenamate
Azacosterol	exifone
Azacyclanol	fendosal
Benzarone	fenpentadiol

Benzbromarone	Frenticlor
Benziodarone	fentonium
Benzilonium	fexofenadine
Bicalutamide	flopropione
Bifluranol	flupentixole
Buclosamide	fluphenazine
Buphenine	flutazolam
Bupheniode	flutropium
Butoctamide	glazionine
Butropium	halofantone
Butylscopolammonium	homofenazine
Cadralazine	hydroxychloroquine
Cafaminol	idebenone
Cafedrine	ifenprodil
Calcitriol	isoxicam
Calusteron	ketobemidone
Pantethonate	lobeline
mazaticol	
mazindol	nitroxoline
mefloquine	omnipressin
meloxicam	oxacoprol
mephenesin	oxitriptan
meptazinol	oxyphenbutazone
metaraminol	piperacetazine
mifepristone	pyritinol
mitopodozide	quinagolide
mitoxantrone	quinidine
monobenzene	suplatast tosylate
nadolol	tioxolone

trifluperidol

trihexyphenidyl (benzhexol)

xipamide

Preferably, the pharmaceutical hydroxy compound is selected from the group consisting of estrogen, estradiol, testosterone, atropine, morphine and mixtures thereof.

5 Atropine is an alkaloid derived from solanaceous plants and used in treatment of poisoning, where exposure to an organophosphate pesticide, insecticide or herbicide prevents nerve transmission resulting in inhibition of secretions, bradycardia, mydriasis, inhibition of gastrointestinal motility, and excitatory effects similar to adrenaline, which at toxic doses can cause death. Atropine is typically 10 used in this situation as an effective antidote as the alkaloid is a competitive antagonist of acetylcholine at muscarinic receptors, reversing muscarinic effects of the organophosphate exposure. Morphine is also an alkaloid and potent analgesic.

15 The "phosphate derivatives of pharmaceutical hydroxy compounds" comprise compounds covalently bound by means of an oxygen to the phosphorus atom of a phosphate group thus forming a carbon –oxygen –phosphorous bond. The oxygen atom is typically derived from a hydroxyl group on the pharmaceutical hydroxy compounds. The phosphate derivative may exist in the form of a free phosphate acid; a salt thereof; a phosphate ester having two molecules of 20 pharmaceutical hydroxy compounds; a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl or substituted alkyl group; or a complex with one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having nitrogen functional groups and proteins rich in these amino acids; or mixtures thereof.

25 Preferred phosphate derivatives of pharmaceutical hydroxy compounds include oestrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof.

For example, a typical mixture of phosphate derivatives of estradiol would include mono-estradiol phosphate derivative and di-estradiol phosphate derivative wherein 30 the amount of mono-estradiol phosphate is no less than equimolar to the amount of di-estradiol phosphate derivative. This mixture of estradiol phosphates may then be complexed with one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having

nitrogen functional groups and proteins rich in these amino acids as disclosed in international patent application no PCT/AU01/01476.

Preferably, the complexing agents are selected from arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:

5

$$\text{NR}^1\text{R}^2\text{R}^3$$

wherein R^1 is chosen from the group comprising straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof;

10

R^2 and R^3 are chosen independently from the group comprising H,

CH_2COOX , $\text{CH}_2\text{CHOHCH}_2\text{SO}_3\text{X}$, $\text{CH}_2\text{CHOHCH}_2\text{OPO}_3\text{X}$, $\text{CH}_2\text{CH}_2\text{COOX}$,

CH_2COOX , $\text{CH}_2\text{CH}_2\text{CHOHCH}_2\text{SO}_3\text{X}$ or $\text{CH}_2\text{CH}_2\text{CHOHCH}_2\text{OPO}_3\text{X}$ and X is

H, Na, K or alkanolamine provided R^2 and R^3 are not both H; and

wherein when R^1 is RCO then R^2 may be CH_3 and R^3 may be

$(\text{CH}_2\text{CH}_2)\text{N}(\text{C}_2\text{H}_4\text{OH})\text{H}_2\text{CHOPO}_3$ or R^2 and R^3 together may be

$\text{N}(\text{CH}_2)_2\text{N}(\text{C}_2\text{H}_4\text{OH})\text{CH}_2\text{COO}^-$.

15 The formation of the complex of the phosphate derivatives of pharmaceutical hydroxy compounds may occur as a separate step in the manufacture process or it may occur in situ in the final topical formulation. For example, the complex of morphine phosphate and lysine may be formed and then added to the carrier to form the topical formulation. Alternatively, morphine phosphate ester may be added to a carrier containing a complexed phosphate entity such as lauryliminodipropionic acid tocopheryl phosphate and there will be some in situ formation of the complex of morphine phosphate and lauryliminodipropionic acid. Phosphorylation may be accomplished by any suitable method. Preferably, the hydroxyl group-containing compound is phosphorylated using P_4O_{10} according to the method in international patent application no PCT/AU00/00452. Excess diphosphate derivatives may be hydrolyzed using methods known to those skilled in the art.

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The term "effective skin-penetrating amount" is used herein to refer to an amount that penetrates the stratum corneum to reach the epidermal and dermal layers of the skin in an amount that is measurably effective in the reduction of one or more symptoms presented by a patient suffering from a skin condition. A person skilled in the art will understand that the actual amount will vary from drug to drug. The effective skin penetrating amount will be sufficient to provide an amount within the therapeutic range of a drug. In some instances, the skin effective penetrating amount will be 1 to 10 times the current therapeutic I.V. dose for a therapeutic drug. For example, an effective skin penetrating amount of estradiol phosphate in

30

35

a topical formulation according to the invention may be 1.2 times the current IV dose of estradiol. For atropine phosphate, the effective skin penetrating amount may be 3 times the current IV dose of atropine. If the drug is currently provided orally, then the effective skin penetrating amount may be a fraction of the current
5 therapeutic ingestible dose because ingestible doses have to allow for immediate elimination by the liver.

The topical formulation of the invention may be any suitable topically applied delivery systems considered by those skilled in the pharmaceutical art as capable of delivering drugs topically on human or other animal skin to achieve a systemic
10 or dermal effect. It includes but is not limited to creams, lotions, gels, emulsions, liposomes, aerosols, patches, poultices, subcutaneous depots, plasters and sustained release systems designed to alter absorption kinetics in favor of zero order release.

The term "transdermal delivery system" is used herein to refer to sustained release
15 systems designed to alter absorption kinetics in favor of zero order release.

The term "acceptable carrier" is used herein to refer to a carrier considered by those skilled in the pharmaceutical art to be useful in topical formulations and transdermal delivery systems capable of being used topically on human or other animal skin. This includes the use of other excipients such as skin penetration
20 enhancers, solvents, surfactants, emollients, preservatives, colorants and fragrances. A person skilled in the art will know what components may be used as the acceptable carrier for the formulations of the present invention. Conventional pharmaceutical processes may be used in making up these common forms of compositions.

25 A preferred carrier for a topical formulation according to the invention comprises a complex of tocopheryl phosphates and complexing agents are selected from arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:



30 wherein R¹ is chosen from the group comprising straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof;
R² and R³ are chosen independently from the group comprising H, CH₂COOX, CH₂CHOHCH₂SO₃X, CH₂CHOHCH₂OPO₃X, CH₂CH₂COOX, CH₂COOX, CH₂CH₂CHOHCH₂SO₃X or CH₂CH₂CHOHCH₂OPO₃X and X is
35 H, Na, K or alkanolamine provided R² and R³ are not both H; and

wherein when R¹ is RCO then R² may be CH₃ and R³ may be (CH₂CH₂)N(C₂H₄OH)-H₂CH₂PO₃ or R² and R³ together may be N(CH₂)₂N(C₂H₄OH)CH₂COO-.

More preferably, the carrier comprises lauryliminodipropionic acid tocopheryl
5 phosphate.

A typical carrier for a topical formulation according to the invention comprises 61.95% deionized water, 5.00% glycerin, 0.05% trisodium EDTA, 0.50% carbomer (Carbopol Ultrez 10), 7.50% lauryliminodipropionic acid tocopheryl phosphate, 2.00% Phenoxol T (cetearyl alcohol and ceteareth-20), 1.00% glyceryl stearate
10 (Emerest 2400), 5.00% isopropyl myristate (Pelemol IPM), 3.50% cetyl ethylhexanoate (Pelemol 168), 3.50% isocetyl behenate (Pelemol ICB), 3.00% oleyl erucate (Cetiol J-600), 0.50% dimethicone (Dow 200,100 cSt.), 5.00% deionized water, 0.50% triethanolamine (99%) and 1.00% Germaben II (propylene glycol, diazolidinyl urea, methylparaben and propylparaben).

15 According to a second aspect of the invention, there is provided a method for improving skin absorption and/or maintaining adequate blood levels for prolonged periods of a pharmaceutical hydroxy compound, the method comprising the step of topically applying a formulation comprising an effective skin-penetrating amount of one or more phosphate derivatives of a pharmaceutical hydroxy compound and
20 an acceptable carrier.

The method according to the second aspect of the invention is carried out by applying a topical formulation according to the first aspect of the present invention.

One aspect of the invention is directed to a method for hormone replacement therapy comprising topically administering to a patient a formulation comprising an
25 effective skin-penetrating amount of one or more phosphate derivatives of estrogen and an acceptable carrier.

An advantage of the present invention relates to the surprising absorption (movement) through the skin of the pharmaceutical hydroxy compound, effectiveness and longer timeframe that a transdermal delivery system can be
30 utilised on a subject.

According to a third aspect of the invention, there is provided use of one or more phosphate derivatives of a pharmaceutical hydroxy compound in a transdermal delivery system to improve administration to a subject of the corresponding pharmaceutical hydroxy compound.

According to a fourth aspect of the invention, there is provided a transdermal delivery system comprising:

- (a) a device for applying a pharmaceutical composition to skin of a subject; and
- 5 (b) one or more phosphate derivatives of a pharmaceutical hydroxy compound in the device.

Preferably, the device is a patch, poultice, gel, cream, plaster or other sustained-release system designed to alter absorption kinetics in towards zero order release.

10 The one or more phosphate derivatives of a pharmaceutical hydroxy compound may be in admixture with one or more suitable diluents or excipients.

According to a fifth aspect of the invention, there is provided a method for delivering a pharmaceutical hydroxy compound to a subject, the method comprising applying a transdermal delivery system according to the fourth aspect of the present invention to a portion of skin of the subject such that the one or 15 more phosphate derivatives of the pharmaceutical hydroxy compound are transported through the skin barrier of the subject and delivered to the blood stream.

According to sixth aspect of the invention, there is provided a method for improving the efficacy of a pharmaceutical hydroxy compound formulation, the 20 method comprising:

- (a) forming one or more phosphate derivatives of the pharmaceutical hydroxy compound; and
- (b) formulating the one or more phosphate derivatives of the pharmaceutical hydroxy compound into a topical formulation; wherein 25 upon administration to the skin of a subject, the one or more phosphate derivatives of the pharmaceutical hydroxy compound has improved efficacy over the corresponding non-phosphated pharmaceutical hydroxy compound formulation.

The present inventors have found that the phosphate derivatives of 30 pharmaceutical hydroxy compounds effectively permeate the dermal layers significantly more than non-phosphated pharmaceutical hydroxy compounds when used without skin enhancers. As there is no need for skin enhancers, there is no skin irritation or erythema when phosphate derivatives of pharmaceutical hydroxy compounds are used.

In order that the present invention may be more clearly understood, preferred forms will be described with reference to the following drawings and examples.

Brief Description of the Drawings

Figure 1: Changes in total estrogens (mean \pm SD) measured in plasma samples obtained from ovariectomised hairless rats to which formulations containing approximately 0.17 μ g of estrogen (E) or estrogen phosphate (EP) were applied.

Figure 2: Percent change in tritiated E vs tritiated EP in ovariectomised hairless rats to which formulations containing tritiated E or EP were applied.

Figure 3: Changes in total testosterone (mean \pm SD) measured in plasma samples obtained from ovariectomised hairless rats to which formulations containing approximately 1.00 μ g \pm 0.02 μ g of T or TP were applied.

Examples

The invention is further explained and illustrated by the following non-limiting examples.

15 Example 1

Twelve grams (0.03 g/mole) of disodium-N-lauryl beta imino dipropionate were dissolved in 88 grams of distilled water to provide a 12% wt/wt clear solution with pH 12. Morphine-3-phosphoric acid ester (11.43 grams (0.03 g/mole)) was slowly added and mixed until uniform. The resulting product was a complex consisting of N-lauryl beta imino dipropionate—morphine (3) phosphate as a 21.03% wt/wt aqueous dispersion. This complex product was formulated via dilution with water preservative buffers together with gelling agents and applied to the skin to elicit transdermal drug delivery.

The complex product may be modified as needed by increasing or decreasing the molar ratio of the disodium—N—lauryl beta imino dipropionate.

Example 2

The transdermal delivery of estradiol and estradiol phosphate in the hairless rat model was evaluated in this example.

Methods

30 **Animals:** 11 female albino hairless rats were ovariectomised under isoflurane-induced anaesthesia and allowed to recover for 10 days prior to experimentation. This allowed clearance of any estrogens from the body.

Blood sampling: Blood samples (500 μ l) were obtained from the tail vein of conscious restrained rats at 0, 1, 2, 4, 8, 16 and 24 hours following application of

both the estradiol (n=5) and estradiol phosphate (n=6) formulations. Blood was collected into EDTA tubes, then centrifuged at 5000 rpm for 10 minutes. Plasma was removed and stored at -80°C until assayed.

5 *Transdermal Formulation Preparation and Application:* estradiol and estradiol phosphate were provided by Tocovite Pty Ltd and prepared at concentrations of 20 µg/ml approximately 1 hour before application in a carrier cream prepared as follows:

PHASE A	W/W
Deionized water	61.95%
Glycerin	5.00
Trisodium EDTA	0.05
Carbomer (Carbopol Ultrez 10) ²	0.50
Lauryliminodipropionic Acid Tocopheryl Phosphate ¹	7.50
PHASE B	
Cetearyl Alcohol (and) Ceteareth-20 (Phenoxyol T) ³	2.00
Glyceryl Stearate (Emerest 2400) ⁴	1.00
Isopropyl Myristate (Pelemol IPM) ³	5.00
Cetyl Ethylhexanoate (Pelemol 168) ³	3.50
Isocetyl Behenate (Pelemol ICB) ³	3.50
Oleyl Erucate (Cetiol J-600) ⁴	3.00
Dimethicone (Dow 200,100 cSt.) ⁵	0.50
PHASE C	
Deionized Water	5.00
Triethanolamine (99%)	0.50
PHASE D	
Propylene Glycol (and) Diazolidinyl Urea (and) Methylparaben (and) Propylparaben (Germaben II) ⁶	1.00
	100.00%

10 1. Vital Personal Care, Incorporated
 2. B.F. Goodrich, Incorporated
 3. Phoenix Chemical, Incorporated
 4. Cognis, Incorporated
 5. Dow-Corning, Incorporated
 6. ISP Corporation

15 Procedure: Combine Phase A items minus the carbomer and lauryliminodipropionic acid tocopheryl phosphate. When a solution is obtained, disperse carbomer in this solution. Begin heating Phase A to 70-75°C with

adequate agitation. Disperse lauryliminodipropionic acid tocopheryl phosphate in carbomer mucilage with sweep agitation. Combine Phase B items and heat to 75-80°C with adequate agitation. With Phase A uniform and at 70-75°C and Phase B uniform and at 75-80°C, add Phase B to Phase A with adequate agitation. Allow 5 AB to cool to 50°C and then add Phase C solution to AB. Continue adequate agitation of ABC until 45°C is reached. Add Phase D to ABC. Continue adequate agitation until 35°C is reached.

10 Estradiol Phosphate (**EP**): 4.3 mg of EP was dissolved in 17.3 ml of acetone (0.25 mg/ml). Twenty μ l was transferred to an Eppendorf tube and the solvent was evaporated in a nitrogen stream. Then 0.999 g of the carrier cream was added, and mixed with a glass rod and centrifuged. This was repeated 5 times. Final concentration = 4.90 μ g/ml.

15 Estradiol (**E**): 6.7 mg was dissolved in 26.8 ml of absolute ethanol (0.25 mg/ml). Twenty μ L was transferred to an Eppendorf tube and the solvent was evaporated in a nitrogen stream. Then 1.003 g of the carrier cream was added, and mixed with a glass rod and centrifuged. This was repeated 5 times. Final concentration = 4.89 μ g/ml.

20 Each formulation was applied to the dorsal skin of an anaesthetised rat in an area of approximately 4 cm^2 marked with an indelible felt tip marker. Application of approximately 30 mg of formulation (containing 0.17 μ g of E or EP) was applied to the site with a curved glass rod applicator. The formulation was 'rubbed' in until it appeared to have been absorbed into the skin, which took between 5-10 min. Any changes in the consistency of the formulation during this procedure were noted. The amount of formulation applied and the area of the application site were 25 weighed for each animal.

Organ Collection: After 24 hr monitoring animals were killed with an overdose of anaesthetic. All organs were removed, weighed and stored at -80°C until assay.

30 **Total Estrogens RIA:** The RIAs were performed using a commercially available total estrogens kit (ICN Pharmaceuticals, catalogue # 07-140205) with 100% cross-reactivities for 17 β -estradiol and estrone. The standard curve range for this assay is 2.5 – 100 pg/ml ($r^2 = 0.943$). Extraction efficiency was determined through a series of spiking assays and was between 90 to 98% using diethyl ether as the extraction solvent for rat plasma and organs. This solvent did not interfere with the assay. Plasma volumes of 100 μ l were used for assay.

Results

Formulation Application: The average areas (\pm SE) to which formulations were applied on the dorsum of the animals were $3.88 \pm 0.03 \text{ cm}^2$ and $3.88 \pm 0.07 \text{ cm}^2$ for the E and EP groups respectively. The average amounts of these formulations applied in the E and EP groups were 0.17 μg .

5 *Total Estrogens in Plasma:* Measurable levels of estrogens (between the standard curve range of 2.5 – 100 pg/ml) were present in both groups of animals with maximum concentrations of 16.63 ± 8.18 (mean \pm SE) pg/ml plasma measured in the E group at 2, 8 and 16 hr post-application and a maximum concentration of 10 49.16 ± 13.21 pg/ml plasma measured at 16 hr post-application in the EP group (Figure 1). Baseline measurements taken at t=0 were subtracted from all values to correct for background levels present in the plasma.

Discussion

This study evaluated the transdermal delivery of EP and E in female hairless rats. 15 The concentration of estradiol in blood was consistently higher when estradiol phosphate was applied over a 24-hour period (statistically significant, $P<0.01$ at 2, 4 and 16 hours). At the equivalent doses that were applied the EP resulted in at least twice the plasma concentration of the hormone compared to the E treatment. This suggests that EP formulated may provide a more effective formulation for 20 delivering E.

Conclusion

The trial demonstrated that useful doses of estradiol may be delivered based on the hairless rat model and it may be inferred from the similarity of the properties of the hairless rat to human skin. Even more surprising, however, was the finding 25 that EP delivered free estradiol in circulating blood and thus estradiol phosphate may prove to be efficacious for hormone replacement therapy.

Example 3

The acute transdermal penetration of ^3H -Estradiol (^3H -E) and ^3H -Estradiol Phosphate (^3H -EP) in the hairless rat model was evaluated in this model.

30 **Methods**

Animals: 6 female albino hairless rats were used in this study (n=3 per treatment group).

35 *Transdermal Formulation Preparation and Application:* ^3H -E and ^3H -EP were provided by Tocovite Pty Ltd and prepared in formula approximately 1 hr before application in the carrier cream used in Example 2.

Twenty μ l of 3 H-E and 3 H-EP were aliquoted into 1 ml Eppendorf tubes. The solvents from both 3 H-E and 3 H-EP were evaporated under a stream of nitrogen. Once completely dry 0.498 g of the carrier cream was added to 3 H-E and 0.502 g to 3 H-EP and mixed with a glass rod and centrifuged for 1 minute. This was 5 repeated 5 times.

Each formulation was applied to the dorsal skin of an anaesthetised rat in an area of approximately 4 cm^2 marked with an indelible felt tip marker. Application of approximately 30 mg of formulation (containing 5 μ g of 3 H-E and 3 H-EP) was applied to the site with a curved glass rod applicator. The formulation was 10 'rubbed' in until it appeared to have been absorbed into the skin, which took between 5 to 10 minutes. A tegaderm (3M) patch was applied to the area to prevent animals from removing the formulation.

Results and Discussion

This study clearly demonstrated that EP was more readily absorbed in comparison 15 to E when transdermally applied (Figure 2). Analysis of individual skin layers was also undertaken in this study and revealed that minimal E or EP remained in the skin 24 hours after application. Higher levels of EP were found in the epidermis and dermis due to higher volumes of the EP moving through the skin during the 24-hour period. This suggests that more of the EP was transported through the 20 skin during the treatment period.

Example 4

The transdermal delivery of testosterone and testosterone phosphate in the hairless rat model was investigated in this example.

Methods

25 *Animals:* 12 Female albino hairless rats were ovariectomised under isofurane-induced anaesthesia and allowed to recover for 15 days prior to experimentation.

Blood Sampling: Blood samples (500 μ l) were obtained from the tail vein of conscious restrained rats at 0, 1, 2, 4, 8, 16 and 24 hr following application of both testosterone (n=6) and testosterone phosphate (n=6) formulations. Blood was 30 collected into EDTA tubes, then centrifuged at 5000 rpm for 10 min. Plasma was removed and stored at -80°C until assay.

Transdermal Formulation Preparation and Application: Testosterone and testosterone phosphate were provided by Tocovite Pty Ltd and prepared in the carrier cream used in Example 2 approximately 1hr before application.

7. A topical formulation according to claim 6 wherein the complexing agents are selected from arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:



5 wherein R¹ is chosen from the group comprising straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof; R² and R³ are chosen independently from the group comprising H, CH₂COOX, CH₂CHOHCH₂SO₃X, CH₂CHOHCH₂OPO₃X, CH₂CH₂COOX, CH₂COOX, CH₂CH₂CHOHCH₂SO₃X or CH₂CH₂CHOHCH₂OPO₃X and X is H, Na, K or alkanolamine provided R² and R³ are not both H; and wherein when R¹ is RCO then R² may be CH₃ and R³ may be (CH₂CH₂)N(C₂H₄OH)-H₂CH₂OPO₃ or R² and R³ together may be N(CH₂)₂N(C₂H₄OH)CH₂COO-.

8. A topical formulation according to claim 7 wherein the complexing agents are complexed with phosphate derivatives of pharmaceutical hydroxy compounds selected from the group consisting of oestrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof.

15 9. A topical formulation according to any one of the preceding claims wherein the carrier comprises a complex of tocopheryl phosphates and complexing agents are selected from arginine, lysine, histadine and tertiary substituted amines, such as those according to the following formula:



25 wherein R¹ is chosen from the group comprising straight or branched chain mixed alkyl radicals from C6 to C22 and carbonyl derivatives thereof; R² and R³ are chosen independently from the group comprising H, CH₂COOX, CH₂CHOHCH₂SO₃X, CH₂CHOHCH₂OPO₃X, CH₂CH₂COOX, CH₂COOX, CH₂CH₂CHOHCH₂SO₃X or CH₂CH₂CHOHCH₂OPO₃X and X is H, Na, K or alkanolamine provided R² and R³ are not both H; and wherein when R¹ is RCO then R² may be CH₃ and R³ may be (CH₂CH₂)N(C₂H₄OH)-H₂CH₂OPO₃ or R² and R³ together may be N(CH₂)₂N(C₂H₄OH)CH₂COO-.

The Claims Defining the Invention are as follows:

1. A topical formulation comprising an effective skin-penetrating amount of one or more phosphate derivatives of one or more pharmaceutical hydroxy compounds and an acceptable carrier.
- 5 2. A topical formulation according to claim 1 wherein the topical formulation is a transdermal delivery system comprising one or more sustained release systems designed to alter absorption kinetics in favor of zero order release.
- 10 3. A topical formulation according to either claim 1 or 2 wherein the pharmaceutical hydroxy compound is selected from the group consisting of estrogen, estradiol, testosterone, atropine, morphine and mixtures thereof.
- 15 4. A topical formulation according to any one of the preceding claims where the phosphate derivative exists in a form selected from the group consisting of free phosphate acid; a salt thereof; a phosphate ester having two molecules of pharmaceutical hydroxy compounds; a phosphatidyl compound wherein the free phosphate oxygen forms a bond with an alkyl or substituted alkyl group; or a complex with one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having nitrogen functional groups and proteins rich in these amino acids; and mixtures thereof.
- 20 5. A topical formulation according to claim 4 wherein the phosphate derivatives of pharmaceutical hydroxy compounds are selected from oestrogen phosphate ester, estradiol phosphate ester, testosterone phosphate ester, atropine phosphate ester, morphine phosphate ester and mixtures thereof.
- 25 6. A topical formulation according to claim 4 wherein the phosphate derivative is complexed with one or more complexing agents selected from the group consisting of amphoteric surfactants, cationic surfactants and amino acids having nitrogen functional groups and proteins rich in these amino acids.

For example, the baseline heart rate of a rat was approx. 350 bpm and increased to 450 bpm within 15 minutes after administration of atropine (either atropine phosphate or atropine sulfate). Approximately two hours later, normal heart rates were restored. This is regarded as a significant change in pulse rate.

- 5 These results show that atropine phosphate is effective to increase pulse rate. It is expected that when provided transdermally similar results will be achieved.

The word 'comprising' and forms of the word 'comprising' as used in this description does not limit the invention claimed to exclude any variants or additions.

- 10 Modifications and improvements to the invention will be readily apparent to those skilled in the art. Such modifications and improvements are intended to be within the scope of this invention.

Testosterone Phosphate (TP): 4.41 mg of TP was dissolved in 15 ml of water and then made up to 100 ml with ethanol. 1 ml was transferred to an Eppendorf tube and the solvent was evaporated under a nitrogen stream. 1.00 g of the carrier cream from Example 2 was added and mixed with a glass rod and centrifuged.

5 This was repeated 5 times.

Testosterone (T): 3.94 mg of T was dissolved in 15 ml of water and then made up to 100 ml with ethanol. 1 ml was transferred to an Eppendorf tube and the solvent was evaporated under a nitrogen stream. 1.00 g of the carrier cream from Example 2 was added and mixed with a glass rod and centrifuged. This was

10 repeated 5 times.

Each formulation was applied to the dorsal skin of an anaesthetized rat in an area of approximately 4 cm² marked with an indelible felt tip marker. Application of approximately 30 mg of formulation (containing 1 µg of T or TP) was applied to the site with a curved glass rod applicator. The formulation was 'rubbed' in until it

15 appeared to have been absorbed into the skin, which took between 5 to 10 min. Any changes in the consistency of the formulation during this procedure were noted.

Results

20 *Formulation Application:* The average amounts of these formulations applied in the T and TP groups were 1 µg ± 0.02 µg.

25 *Total Testosterone in Plasma:* Measurable levels of testosterone (between standard curve range 2.5 – 100 pg/ml) were present in both groups of animals with maximum concentrations of 30.90 ± 11.00 (mean ± SD) pg/ml plasma measured in the T groups at 1, 8 and 16 hr post-application. Baseline measurements were taken at t=0 and these values were subtracted from all values to correct for background levels in the plasma (Figure 3).

Discussion

The concentration of testosterone in blood increased when both testosterone and testosterone phosphate was applied.

30 **Example 5**

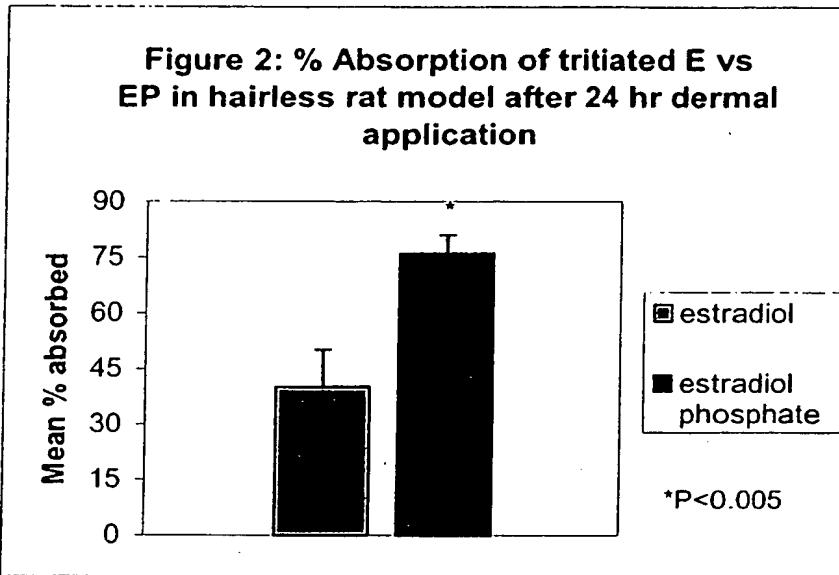
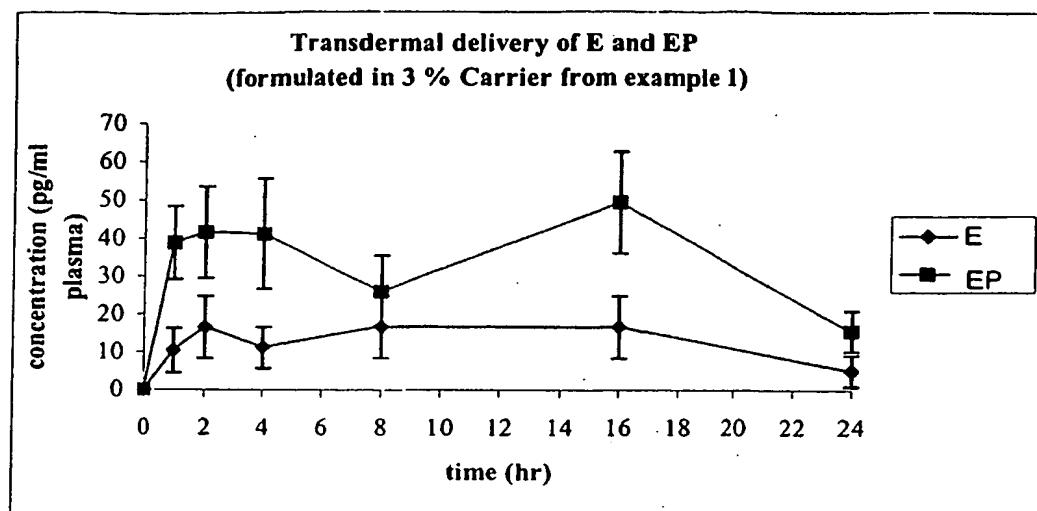
The efficacy of atropine phosphate when compared to atropine sulfate was investigated in this example.

Atropine sulfate and atropine phosphate formulated in phosphate buffer and given intravenously (IV) each to two rats at 2mg/kg resulted similar increases in heart

35 rates.

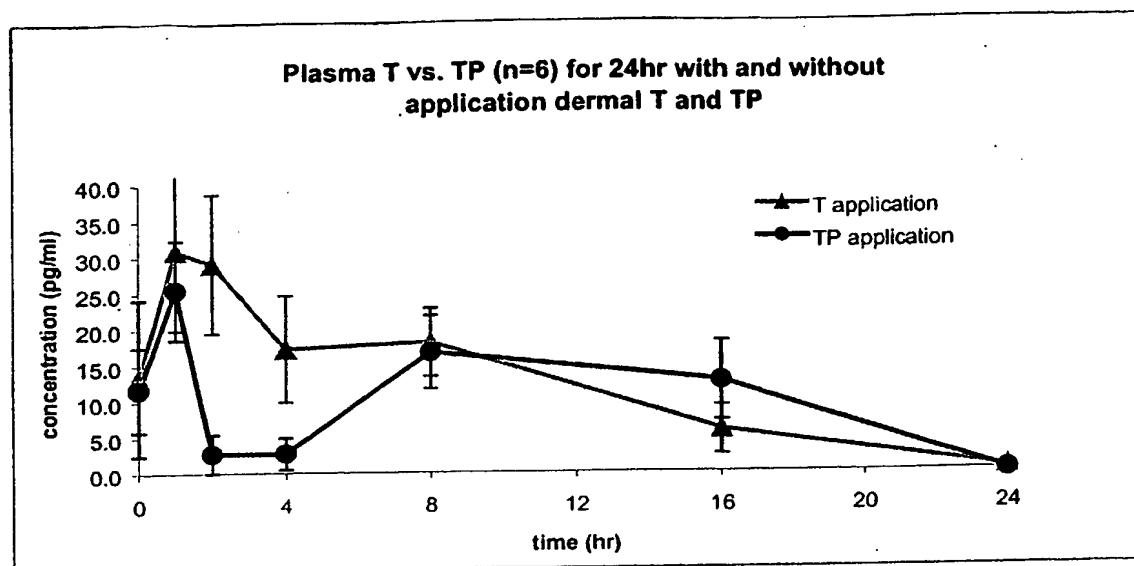
10. A topical formulation according to claim 9 wherein the carrier comprises lauryliminodipropionic acid tocopheryl phosphate.
11. A topical formulation according to claim 10 wherein the carrier comprises 61.95% deionized water, 5.00% glycerin, 0.05% trisodium EDTA, 0.50% carbomer, 7.50% lauryliminodipropionic acid tocopheryl phosphate, 2.00% cetearyl alcohol and ceteareth-20, 1.00% glyceryl stearate, 5.00% isopropyl myristate, 3.50% cetyl ethylhexanoate, 3.50% isocetyl behenate, 3.00% oleyl erucate, 0.50% dimethicone, 5.00% deionized water, 0.50% triethanolamine (99%) and 1.00% propylene glycol, diazolidinyl urea, 10 methylparaben and propylparaben.
12. A method for improving skin absorption and/or maintaining adequate blood levels for prolonged periods of a pharmaceutical hydroxy compound, the method comprising the step of topically applying a formulation comprising an effective skin-penetrating amount of one or more phosphate derivatives of a pharmaceutical hydroxy compound and an acceptable carrier.
13. A method for hormone replacement therapy comprising topically administering to a patient a formulation comprising an effective skin-penetrating amount of one or more phosphate derivatives of oestrogen and an acceptable carrier.
- 20 14. Use of one or more phosphate derivatives of a pharmaceutical hydroxy compound in a transdermal delivery system to improve administration to a subject of the corresponding pharmaceutical hydroxy compound.
15. A transdermal delivery system comprising:
 - (a) a device for applying a pharmaceutical composition to skin of a subject; and
 - (b) one or more phosphate derivatives of a pharmaceutical hydroxy compound in the device.
- 25 16. A transdermal delivery system according to claim 15 wherein the device is a patch, poultice, gel, cream, plaster or other sustained-release system designed to alter absorption kinetics in towards zero order release.
- 30

17. A method for delivering a pharmaceutical hydroxy compound to a subject, the method comprising applying a transdermal delivery system according to either of claim 15 or 16 to a portion of skin of the subject such that the one or more phosphate derivatives of the pharmaceutical hydroxy compound are transported through the skin barrier of the subject and delivered to the blood stream.
5
18. A method for improving the efficacy of a pharmaceutical hydroxy compound formulation, the method comprising:
 - (a) forming one or more phosphate derivatives of the pharmaceutical hydroxy compound; and
10
 - (b) formulating the one or more phosphate derivatives of the pharmaceutical hydroxy compound into a topical formulation; wherein upon administration to the skin of a subject, the one or more phosphate derivatives of the pharmaceutical hydroxy compound has improved efficacy over the corresponding non-phosphated pharmaceutical hydroxy compound formulation.
15

Figure 1

2/2

Figure 3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU02/01686

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.?: A61K 031/045,031/66, 047/42; A61P 25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DWPI, CA: (phosphat+ OR phosfat+) AND (transdermal OR percutaneous OR transcutaneous)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/21440A (Alpha-Therapeutics Inc. et al.) 18 July 1996 See whole document	1, 2, 4, 12, 14 to 18
X	WO 92/08459A (Kabi Pharmacia AB) 29 May 1992 See whole document	1 to 5, 12, 14 to 18
X	WO 00/71125A (LTS Lohmann Therapie-Systeme AG) 30 November 2000 See whole document	1 to 5, 12, 14 to 18

Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent but published on or after the international filing date

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"&" document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
31 January 2003

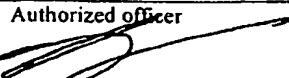
Date of mailing of the international search report

11 FEB 2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU02/01686

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 00/59475A (Lipocene Inc.) 12 October 2000 See whole document	1, 2, 4, 12, 14 to 18
X	WO 91/17987A (SmithKline & French Laboratories Limited) 28 November 1991 See whole document	1, 2, 4, 12, 14 to 18
X	Derwent abstract Accession No.94-103911 JP 06048962A (Morimoto Y) 22 February 1994 Abstract	1, 2, 4, 12, 14 to 18
X	EP 0574255B1 (Indena S.p.A.) 5 March 1997 See whole document	1, 2, 4, 12, 14 to 18
X	WO 93/24131A (Procter & Gamble Pharmaceuticals Inc) 9 December 1993 See whole document	1, 2, 4, 12, 14 to 18
X	US 5,374,645A (KURIHARA-BERGSTROM, Tamie et al.) 20 December 1994 See whole document	1 to 5, 12, 14 to 18
X	WO 95/34303A (Arcturus Pharmaceutical Corporation) 21 December 1995 See whole document	1, 2, 4, 12, 14 to 18
X	WO 96/20715A (Perstorp AB) 11 July 1996 See whole document	1, 2, 4, 12, 14 to 18
X	WO 96/29336A (Medical Research Council et al.) 26 September 1996 See whole document	1, 2, 4, 12, 14 to 18
X	WO 97/35591 (Inspire Pharmaceuticals Inc.) 2 October 1997 See whole document	1, 2, 4, 12, 14 to 18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU02/01686

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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WO	9208459	AU	89381/91	CA	2095223	EP	557385
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		EP	379045	EP	453505	EP	634179
		HK	1006155	NL	9020159	PT	92830
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		EP	592481	SG	43349	WO	9219451
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INTERNATIONAL SEARCH REPORT

International application No.

Information on patent family members

PCT/AU02/01686

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		IL	105838	IL	105835	IL	105839
		MX	9303242	MX	9303243	MX	9303246
		NO	944498	NO	944516	NO	944515
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		ZA	9303768	ZA	9303800	US	5770586
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		NZ	253525	SG	47593	SK	1443/94
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Form PCT/ISA/210 (citation family annex) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU02/01686

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				NZ	332426

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